Canadian Regulatory Perspective on Subsequent-Entry Biologics (Biosimilars)

Anthony Ridgway, Ph.D.
Senior Regulatory Scientist
Biologics & Genetic Therapies Directorate
Health Canada

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Presentation Outline

- **“Comparability”, key elements and current guidance**
- **Subsequent-Entry Biologics (Biosimilars): issues, market musings, regulatory approach**

Comparability

The Question

Product of Process X

Product of Process Y

Comparability
Extent of Studies

- Stage/extent of changes
- Impact on the product
- Analytical capability
- Link between quality criteria and safety and efficacy

ICH Quality - Biotechnology

Q5 A Viral Safety

Q5 B Genetic Stability

Q5 C Product Stability

Q5 D Cell Substrates

Q6 B Product Specifications

Q5 E Comparability

(S6 Safety Studies)

ICH Q5E - General Principles

The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change products are identical; but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

Comparability
Key Elements

- Characterization
- Specifications
- Validation
  - changes to materials or process

Characterization
ICH Q6B

- Chemical structure
- Physicochemical properties
- Biological activity
- Purity
- Impurities
- Quantity

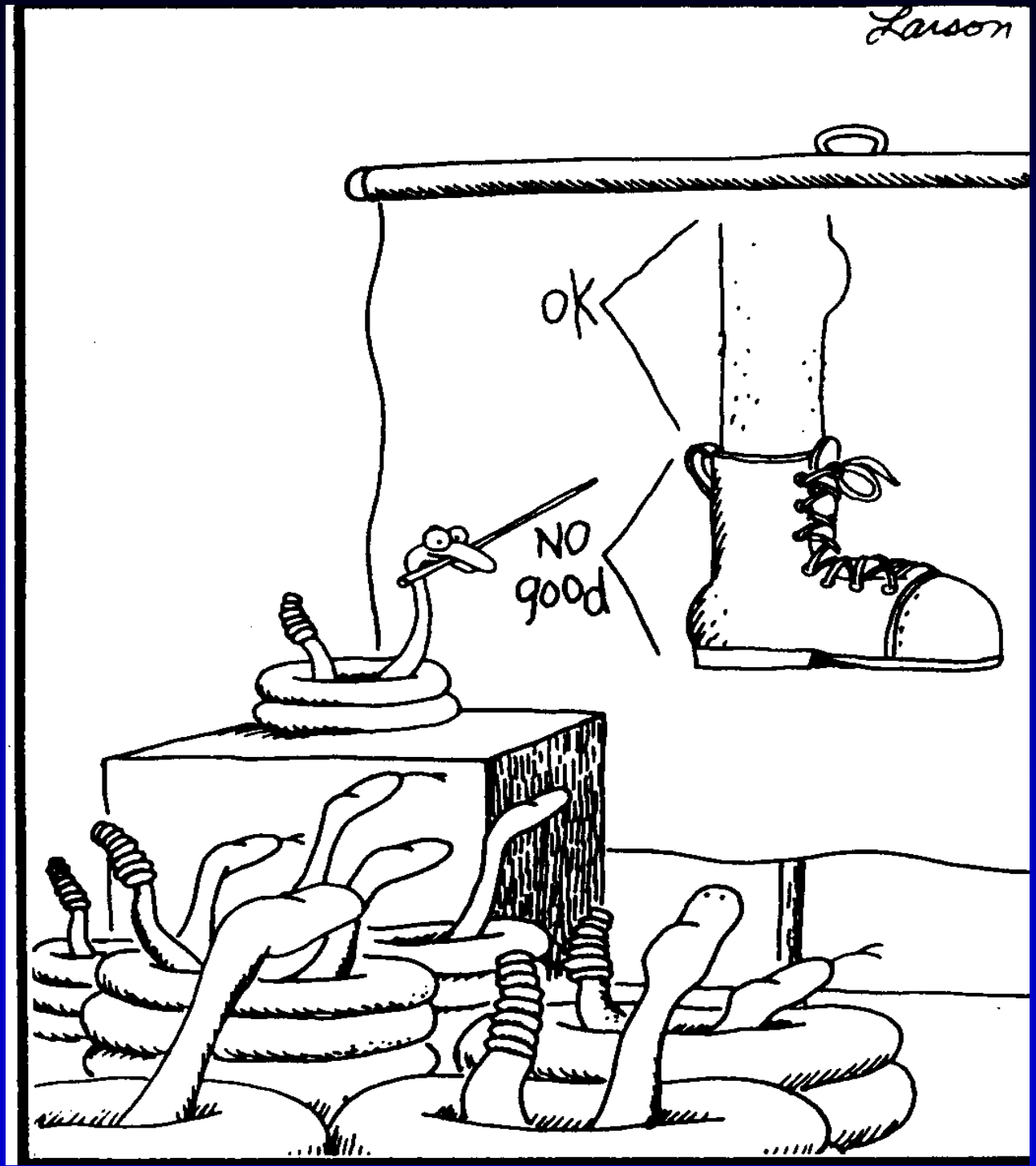
Characterization
Purity/Impurity Profile

Drug substance = Multiple entities

- Desired product (microheterogeneity)
- Product-related substances

- Product-related impurities
- Process-related impurities

- Contaminants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Comparability
Additional Testing

- Tests specifically directed at fully evaluating the impact of the change on the product
- In-process assays at the manufacturing steps which are most likely affected by the manufacturing change

Comparability

Clinical Considerations

bridging study vs larger trial

- Indication
  - mode of action
  - outcome measures
- Dosing and Patient Response
  - units of activity
  - route of administration
  - narrow therapeutic index
- Safety Versus Efficacy
  - immunogenicity
  - active ingredient vs impurities

Immunogenicity Issues

- Most biopharmaceuticals induce antibodies
- Manufacturing changes can cause unexpected changes in immunogenicity
- Current analytical methods cannot fully predict biological properties
- Immunogenicity of biopharmaceuticals may have serious clinical consequences

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- **Subsequent-Entry Biologics (Biosimilars): issues, market musings, regulatory approach**

What's in a Name?

- ✗ Generic biologic
- ? Second-entry biologic
- ? Multi-source biologic
- ✓ Biosimilar medicinal product
- ✓ Follow-on biologic (protein product)
- ✓ Subsequent-entry biologic

Demonstration of Comparability
(following manufacturing change)

- The quality attributes of the post-change product are highly similar to those of the pre-change product
- Pre-clinical and clinical data obtained with earlier versions of the drug product are relevant to the post-change product
- The manufacturing changes do not have an adverse effect on the quality, safety or efficacy of the drug product

Comparability Challenges: Biologic vs Chemical Drug

- Size and complexity of the “desired product”
- Heterogeneity (inherent, process-related, etc.) and the purity/impurity profile of drug product
- Adventitious agents
- Limitations of methods for characterization
- Immunogenicity

Innovator Advantages for Demonstration of Comparability for a Biologic

- Broad experience with product and process
- Availability of drug substance
- Linkages between quality attributes of product and clinical safety and efficacy are known
- Ability to examine any observed change in the context of the range of historical values for clinical trial materials

Clinical Data

Source and Use

- Generated from new studies
- Published in scientific journals

Application of regulator's experience including proprietary sources:

- ✓ Concerns about safety and efficacy
- ? Comfort with safety and efficacy


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Market Musings

- How many national comparators?
- How many competitors and how much competitive advantage ? Blockbusters only ?
- Patients, formularies, pharmacists & social medicine
- “Second generation” competition and “standard of care”

Market Musings

Reference Products (Comparators)

(Generics claim equivalence to a nationally-approved innovator product)

- Biosimilars need comparability to an innovator
  - If nationally approved – how many for global market?
    - Cost of many comparisons *vs* full clinical package?
  - Is chosen comparator still marketed in country?
    - No? - Still comparable to originally approved version?

Competitive advantage?

- Production costs (*versus* innovator)
  - Facilities, equipment, materials, QC/QA, personnel
  - Regulatory requirements (e.g. for process changes)
- Will costs limit # of follow-on sponsors per drug target?
  - Blockbuster targets only?
- Will innovators drop prices to compete?

Market Musings

Formularies, pharmacists & social medicine

- Uninsured patients make good generics consumers but may choose not to pay 80-90% for a biosimilar (whereas Health Plan Managers might)
- Social medicine Drug Formularies prefer generics and would endorse cheaper biosimilars

(Generics may be substituted by pharmacists)

- For innovator, comparable = substitutable (same drug) but for biosimilars, it may not be so. There are scientific and pharmacovigilance issues. Regulatory decision may distinguish between comparable and substitutable, or restrict decision to physician

Market Musings

2nd generation biologics & "standard of care"

- Why choose an old-tech drug for a serious or life-threatening illness?
  - For the uninsured, price may force decision.
  - Health Plan Managers may try to keep costs down
  - Social medicine engenders cost-saving approaches

- However, if the 2nd generation biologic becomes the "standard of care", the 1st generation biosimilar may face hard times in affluent countries.

The Regulatory Pathway Dilemma

- Approach and set of requirements for less complex products will be inadequate for complex products

- Approach and set of requirements for complex products may be excessive for less complex products

Furthermore, clinical parameters (indication, posology, therapeutic index, etc.) influence data requirements

Therefore:

- Detailed guidance must be specific to product or class

- Regulatory approach must be case-by-case

Specific & Related Activities at Health Canada

- Regulation of SEBs is possible within the scope of current regulations. “Outline Document” on the Canadian regulatory approach to SEBs has been made available since 1999.
- “Fact Sheet” on SEBs posted to HC website, July, 2006.
- Work is ongoing to address any impediments to a clearer and more fully described regulatory framework for SEBs and to develop more detailed scientific/clinical guidance.
- External Consultation/Workshop, February 13-14, 2008.
- New authorities and product-life-cycle approaches relevant to a distinct regulatory framework for SEBs are captured within the current, broader initiative on “Progressive Licensing”.

Subsequent-Entry Biologics
Canadian Perspective

- There are no generic biologics
- Examined on a case-by-case basis
- Full chemistry & manufacturing data required
  - plus comparability study with “reference product”
- Clinical data is required
  - extent of clinical data is negotiable
- One indication will not support all indications
  - However - same mechanism of action + rationale ….. ?
- Not interchangeable/substitutable
  - Scientific issues, pharmacovigilance issues


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